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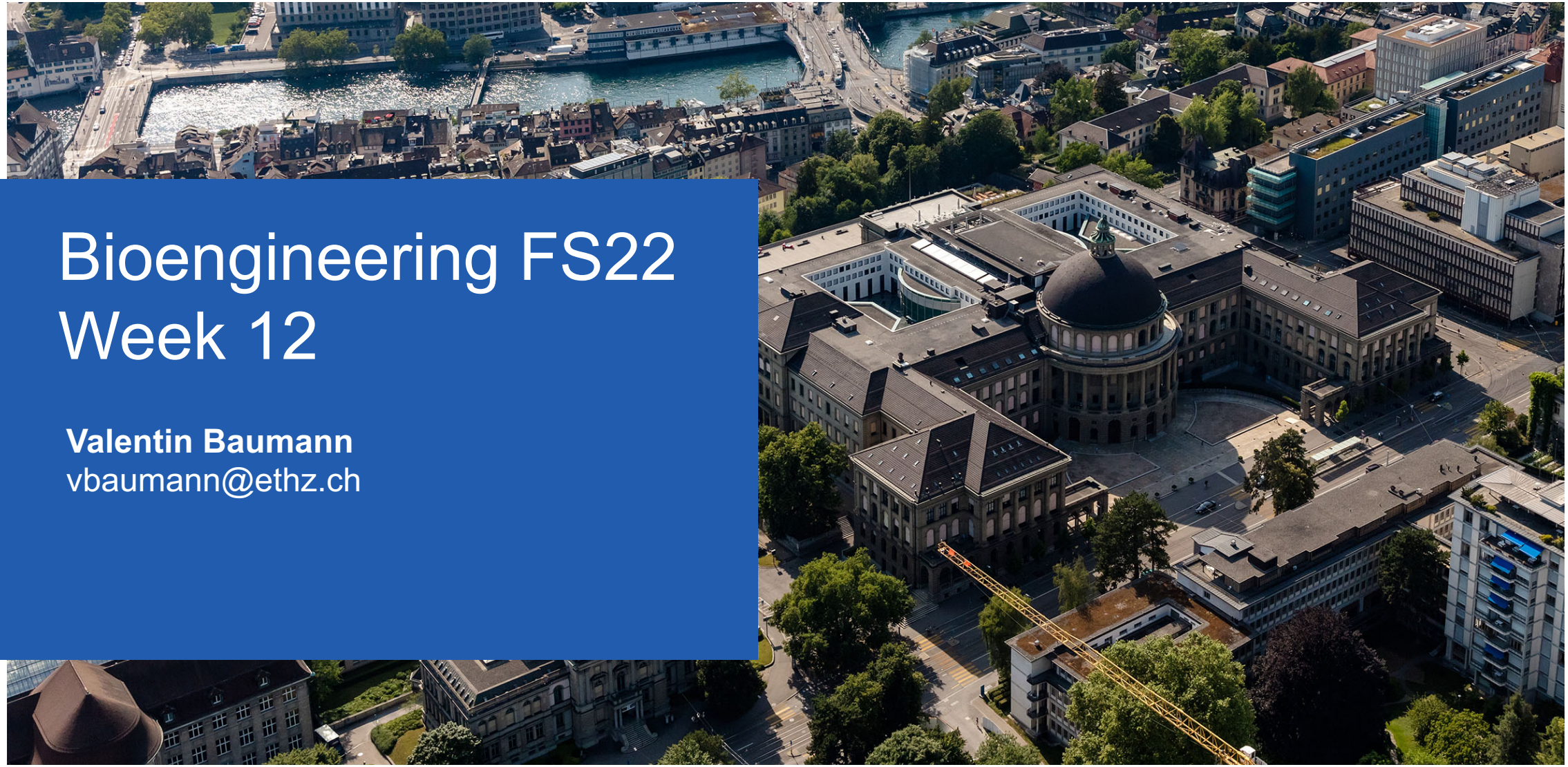

Bioengineering FS22
Week 12

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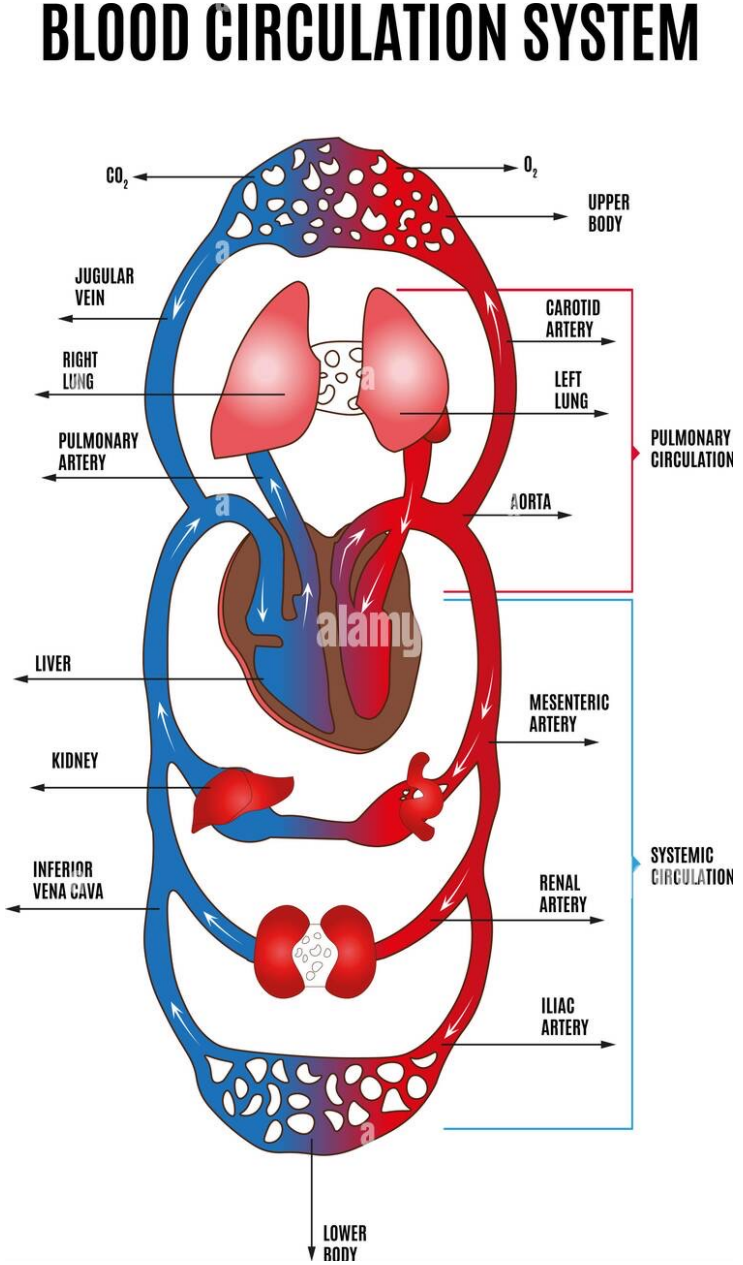
Agenda heute

1. **Blood**
2. **Pathomechanisms**
    1. Cancer
    2. Atherosclerosis
3. **Wound healing (part 500)**
    1. Haemostasis
    2. First-Line Tissue Repair

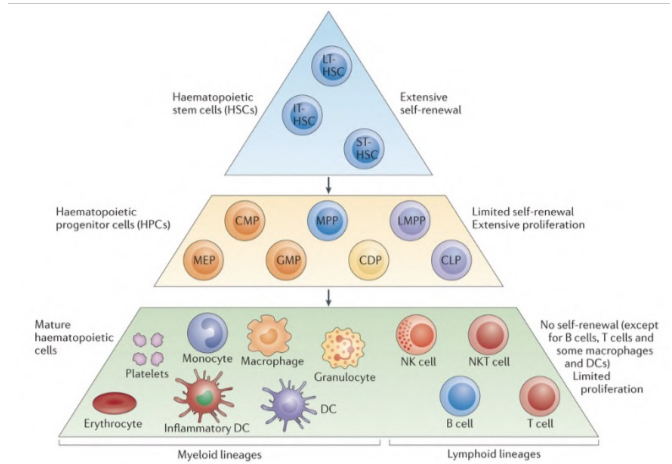
Blood - Introduction

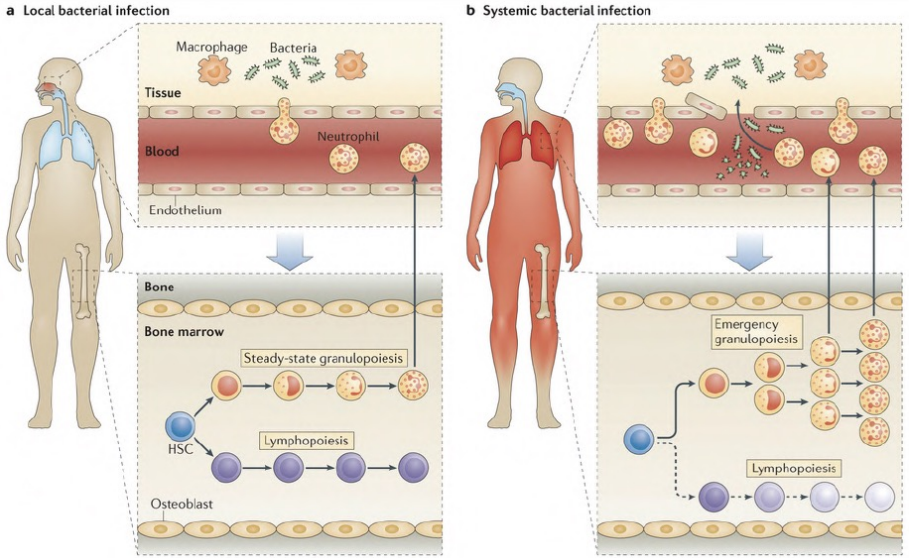
- Distribution of nutrients and hormones throughout the body via the arteries, removal of wate products from tissues via the veins. Another important function is the regulation of the temperature of the body.
- **Blood circulation:**
  Heart – Aorta – Arteries – Arterioles – Capillaries – Venules – Veins – Heart – Lung – Heart – Aorta ...
- **Capillaries** are the place where gas exchange in the periphery takes place and all cells lie within 10-100µm of the closest **capillary** (else they would die). This short distance allows for the diffusion of O2, CO2 and other substances – this diffusion is driven by the **concentration** and **partial pressure gradient**.
- The volume of blood corresponds to about 8% of a persons body weight and blood is a complex suspension (liquid with solid particles). The plasma is the liquid in blood, and while it has a similar density to water, it is 6 times more viscious



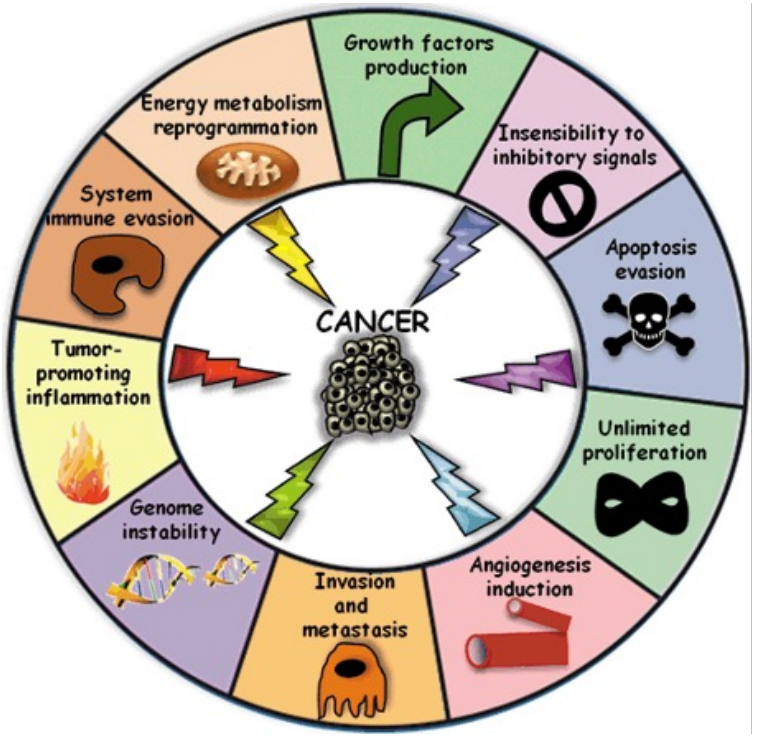
Blood - Hematopoiesis

- The process where hematopoietic stemcells (HSCs) differentiate into the many different types of blood cells.
- It takes place in the bone marrow and its main function is to ensure the continuous supply of blood cells, since their lifespan is quite short and thus the turnover is quite high.
- **Basic cell types**:
  - **Erythrocytes** (Red blood cells, 95% of solids) – transport blood gas
  - **Leukocytes** (White blood cells, 0.15% of solids) – immune system
  - **Thrombocytes** (Platelets, ~ 5 % of solids) – coagulation

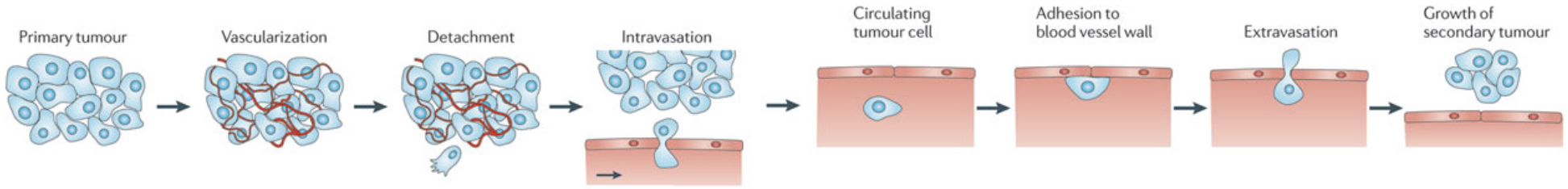




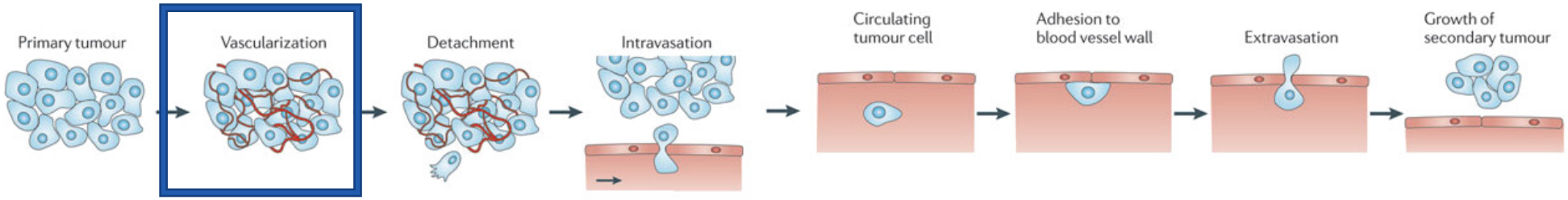
Pathomechanism - Cancer



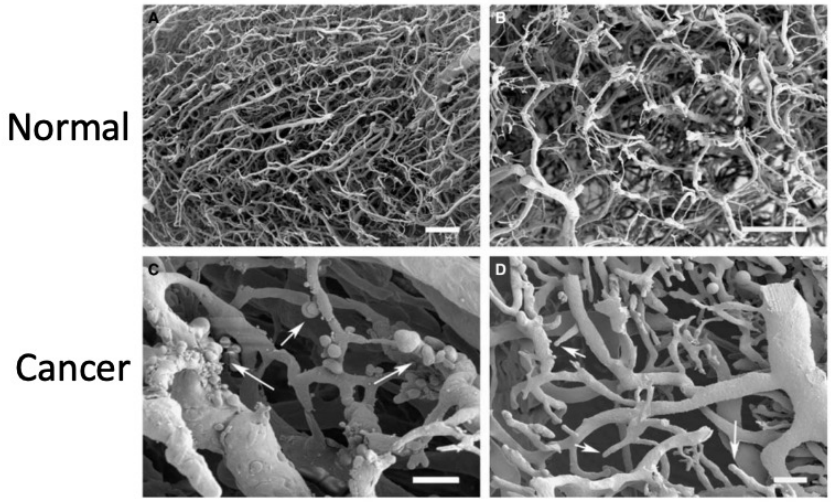
- **Cancer** can arise in every cell of the body, and it usually driven by multiple **mutations**. Those mutations arise due to chemicals, diet and lifestyle, infection, radiation or are inherited (genetics)
- Cancerous cells are characterised by *uncontrolled cell growth, resistance to apoptosis, limitless replication potential, invasion of nearby tissues, evasion of the immune system* and *activation of the vascularisation of the host*.
- The formation of a tumour is quite similar to the failed healing of connective tissue – which cells are now the most important when it comes to the progression of cancer? Stromal cells or epithelial cells?
- One major hallmark of cancer is metastasis – spreading of tumour cells from one part of the body to another. This is what makes cancer so dangerous!



Pathomechanism – Cancer Transition and Vascularisation

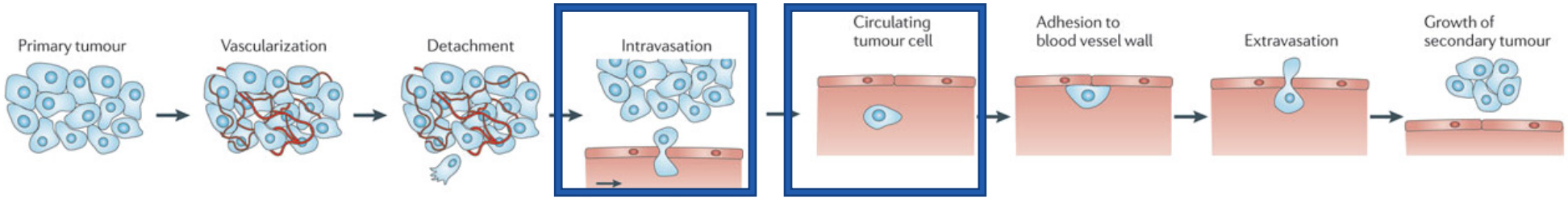


- **Epithelial-Mesenchymal-Transition**: Epithelial cells acquire mesenchymal characteristics (loss of cell junctions, apical-basal polarity, reorganisation of cytoskeleton, adjustment of signalling programs and shift in gene expression) during embryonal development, wound healing and tissue remodelling and cancer progression. In contrast to epithelial cells, mesenchymal cells are not as tightly connected which allows them to migrate more easily.
- **Vascularisation**: formation of fragile, leaky and disorganised blood vessels by four mechanisms:
  - **Angiogenesis**: expansion of existing vessels
  - **Vasculogenesis**: de novo formation of blood vessels from circulating endothelial precursor cells
  - **Transdifferentiation**: cancer cells give rise to functionally deficient endothelial cells
  - **Vascular mimicry**: cancer cells form capillary-like structures without endothelial cells

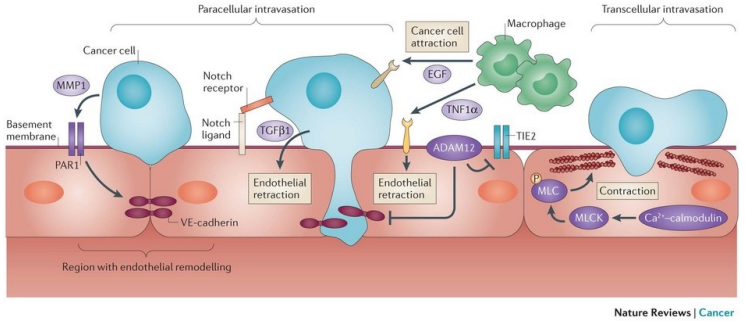


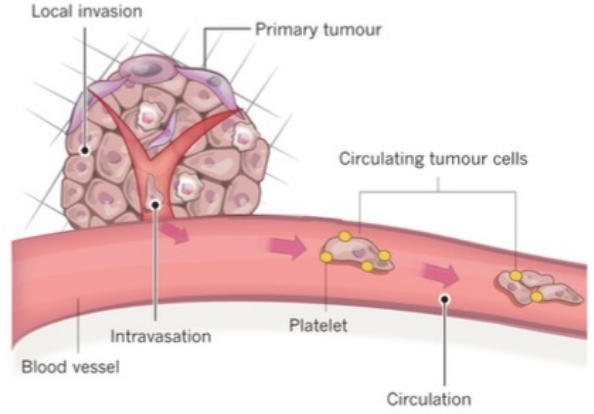
[Silvan et al., 2010]

Pathomechanism – Cancer Intravasation and Circulation

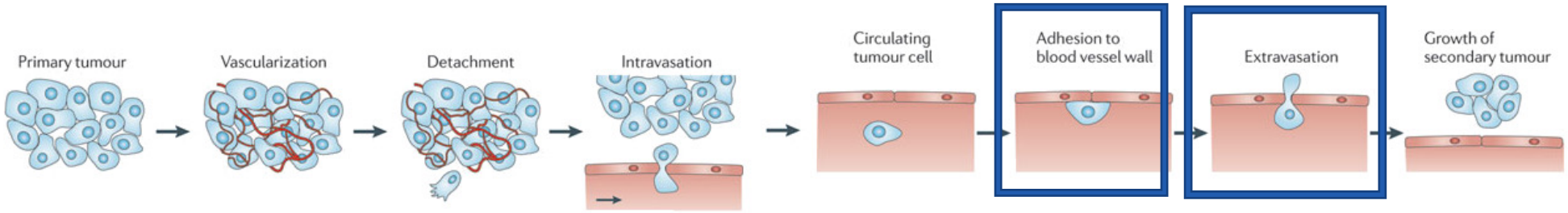


- **Intravasation**: Entry of cancer cells into blood vessels. Cancer cells can enter the circulation either paracellularly or transcellularly. The latter is accompanied by rapid cytoskeletal and membrane remodelling, which creates a transitory structure, that then allows the crossing of the endothelial barrier.
- **Circulating phase**: The tumour cells in the circulation need to adapt to their new environment (no cell-cell contact) and also their morphology as to not be killed by immune cells or stresses in the blood stream. In order to evade immune recognition, they need to be small, have larger nuclear-cytoplasmatic ratios and a softer cortex.

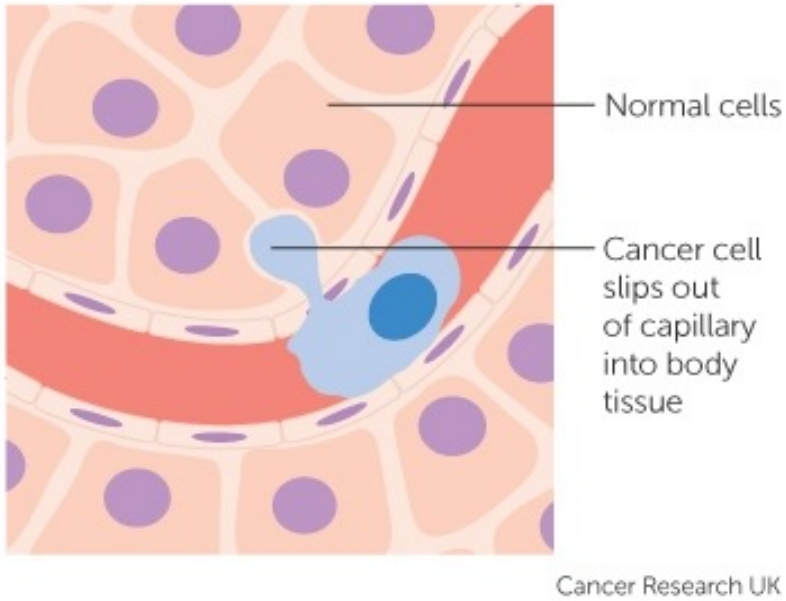




Pathomechanism – Cancer Adhesion and Extravasation

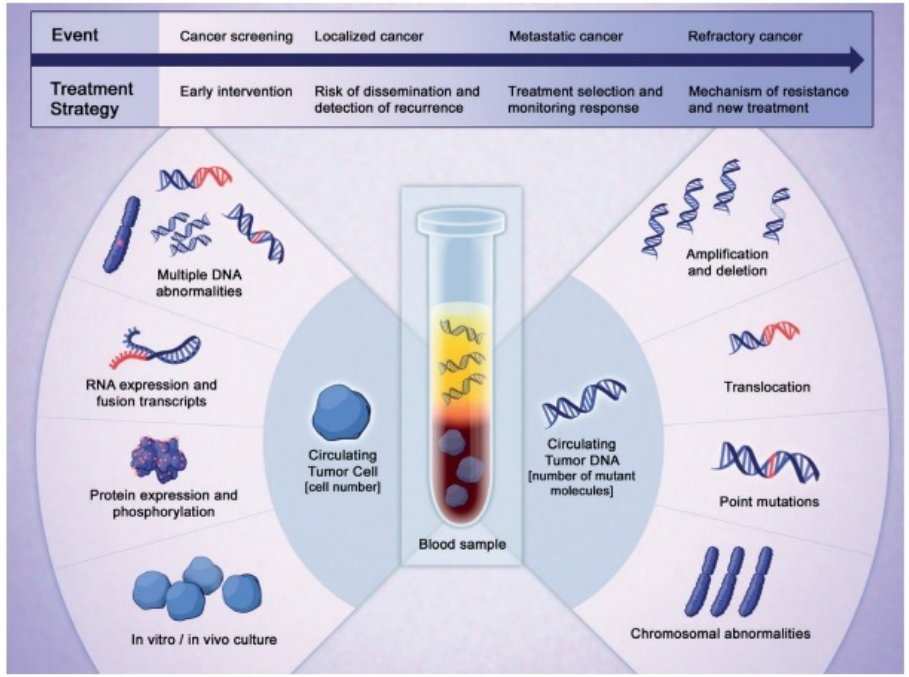


- **Adhesion**: same concept as the adhesion of leukocytes from week 9, slide 8.
- **Extravasation**: The cancer cells „slip“ out of the capillary and into the tissue – the tissue and cancer cell need to be compatible in order for a metastasis to take place! Also once in the tissue, a reversion of the EMT, **MET**, needs to take place, in order for the cells to fit into the new tissue and form the bulk of the new tumour mass.



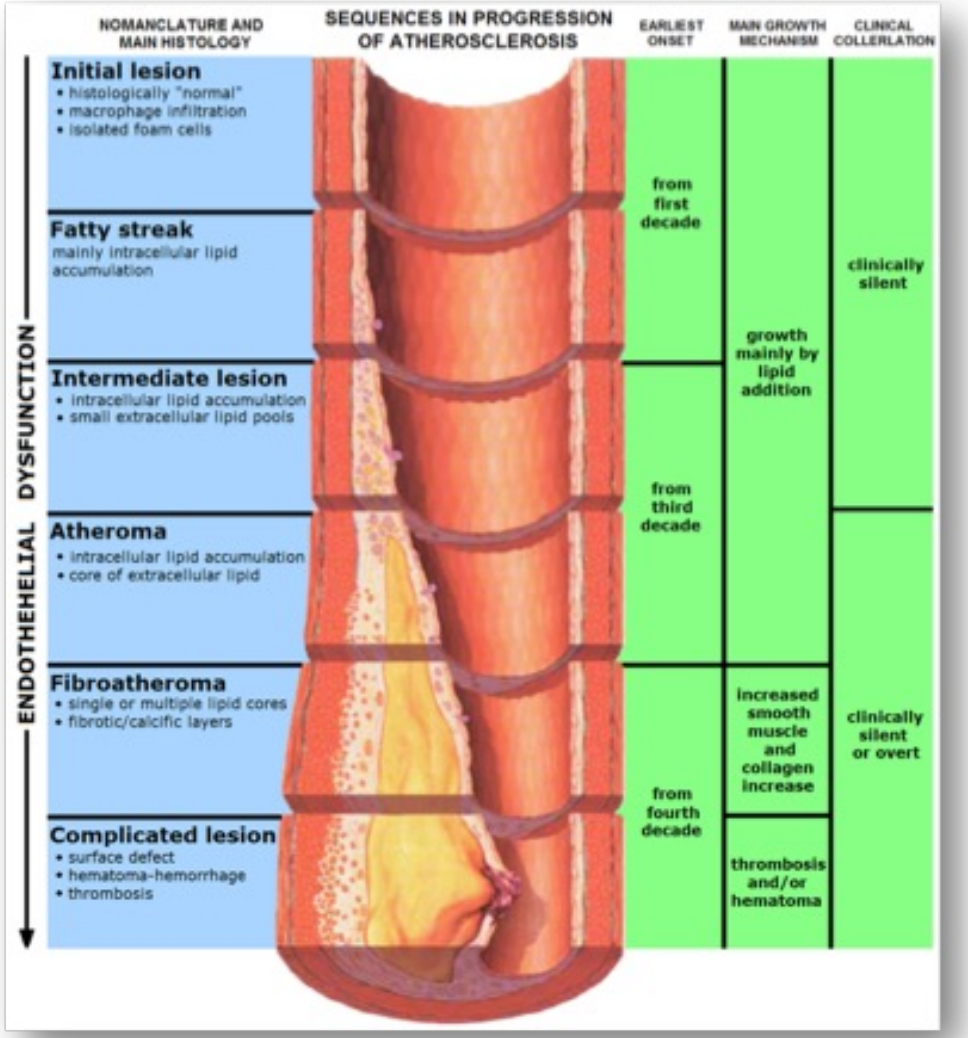
Pathomechanism – Cancer Treatment

- **Surgery**: partial or total removal of the solid malignancy. It the most efficient approach, specially when together with chemotherapy (before, after or both).
- **Radiation**: it can be applied externally or internally (by the use of capsules or injections).
- **Chemotherapy**: different compounds, which have shown selective activity against cancer cells can be used to reduce the size of the solid tumour and to reduce the metastatic ability of the released cells.
- **Immunotherapy**: a number of approaches using antibodies, cytokines, or vaccines have been successfully tested for the treatment of cancer.



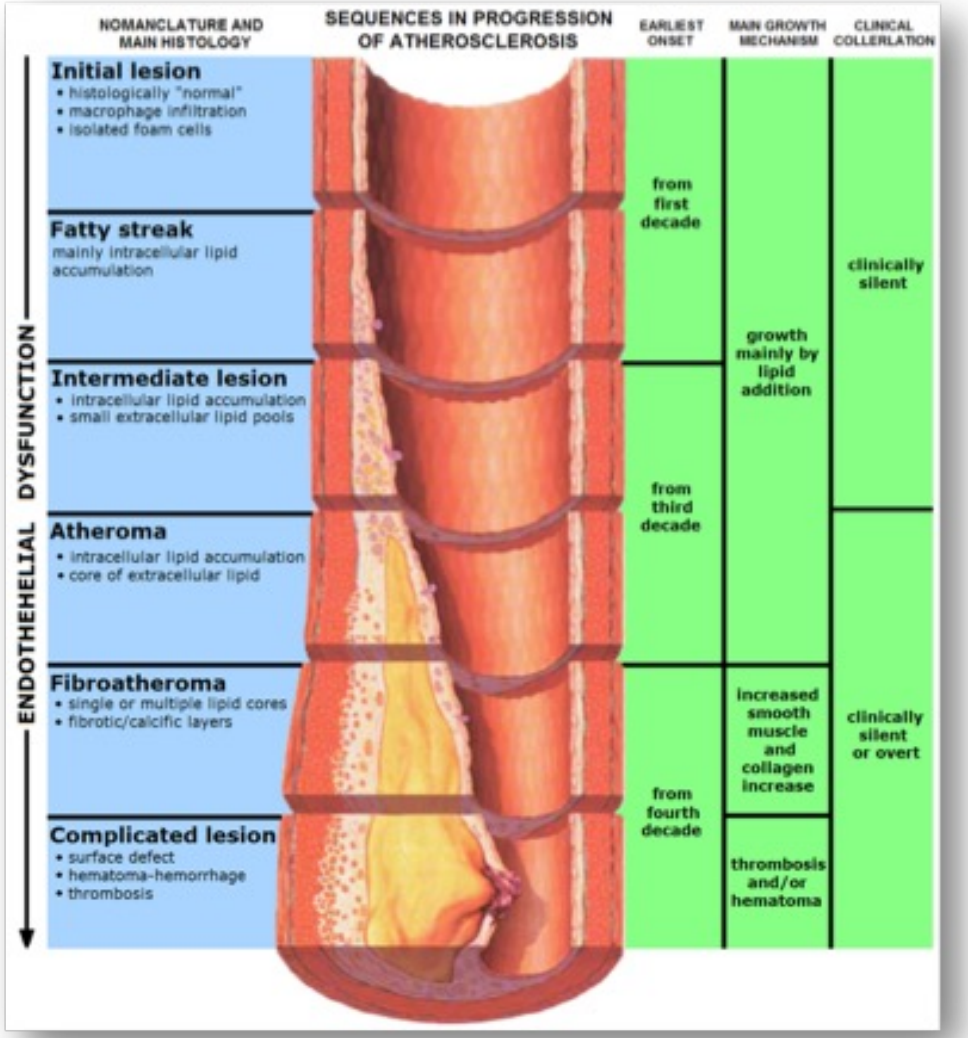
Pathomechanism - Atheroscleorsis

- **Atheroscleoris** is the abnormal remodelling of blood vessel walls and the deposition of fatty acid residues -> restriciton of blood flow. It generally occurs in the carotid arteries, coronary arteries, abdomical aorta and ilio-femoral arteries.
- It is a slow, progressive disease and it is driven by multiple factors:
  - **Biochemical**: high cholesterol, high triglycerides and diabetes
  - **Biological**: inflammation and micro-damages
  - **Mechanical**: hemodynamic factors
- Since there are multiple factors, there are also multiple cells that are involved:
  - **Circulatory**: Leukocytes and monocytes
  - **Resident Tissue Cells**: Endothelial cells (intima), smooth muscle and fibroblasts (externa)



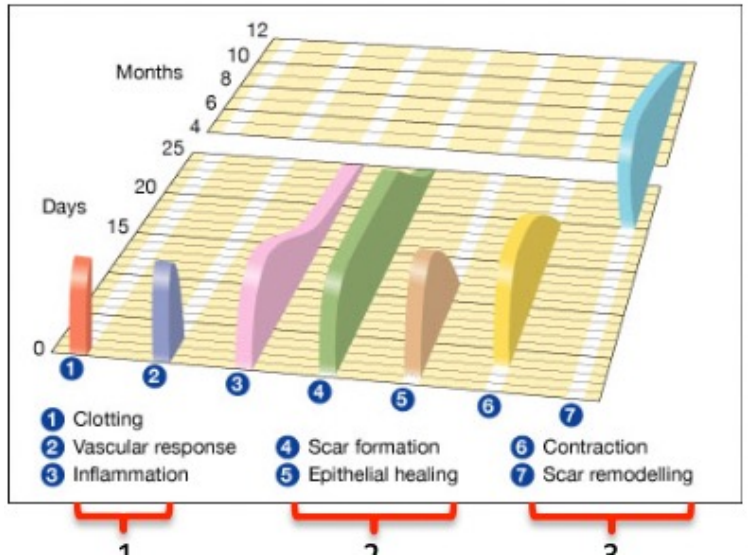
Pathomechanism - Atheroscleorsis

- The **sequential process** of Atherosclerosis can be summarised with the following steps:
  - Lipid deposition
  - Oxidation and inflammation
  - Macrophage activation -> Foam cells
  - Plaque initiation (Foam cell -> Lipid Corea -> Fibrous cap (Collagens and elastins; calcium)
  - Arterial remodeling
  - Plaque rupture dislodgement
  - Contact between lipid core and blood
  - Healing like processes including cycles of tear and repair



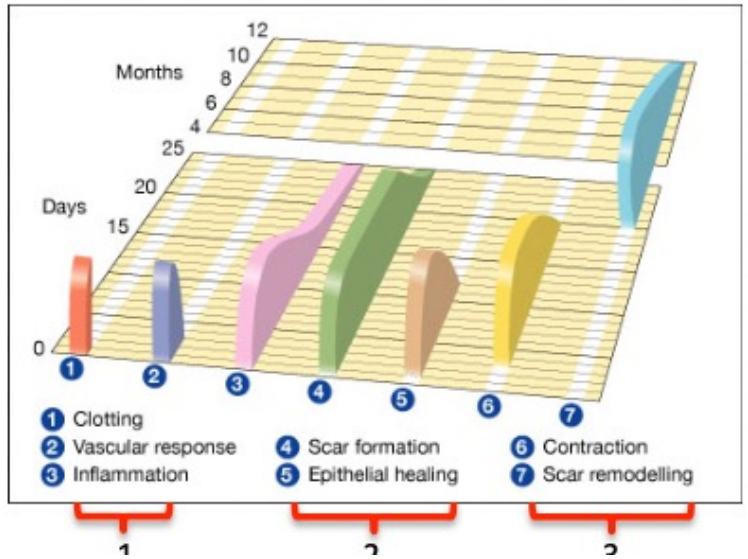
Introduction to Wound Healing – Phases of Wound Healing

- **Phase I**: *Blood cell product*s, aka platelets, very *temporary matrix scaffold* (fibrin), *stimulatory proteins* which recruit vascular and other tissue related stem cells, macrophages and immune cells as well as fibroblasts.
- **Phase I-II**: Granulation tissue forms (mixture of all required players: stem cells, immune cells, other cells, fibronectin, smaller collagens and proteoglycans)
- **Phase II-III**: Revascularisation (vascular modelling) and vascular remodelling (layer collagens, laminin)
- **Phase III**: Scar tissue remodelling (towards normal tissue). Optimal cell types and optimal matrix (usually no or a small amount of fibronectin, fewer smaller and collagens and proteoglycans and more larger collagen and elastin) are used.
- **Clotting -> vascular response -> inflammation -> scar formation -> epithelial healing -> contraction -> scar remodelling.**



Introduction to Wound Healing – Phases of Wound Healing

- **Phase I:** *Blood cell product*s, aka platelets, very *temporary matrix scaffold* (fibrin), *stimulatory proteins* which recruit vascular and other tissue related stem cells, **macrophages and immune cells** as well as fibroblasts.
- The fact that macrophages and immune cells are involved indicates that one of the first steps is **inflammation**.
- Apart from inflammation, clotting and the vascular response are also part of phase I.



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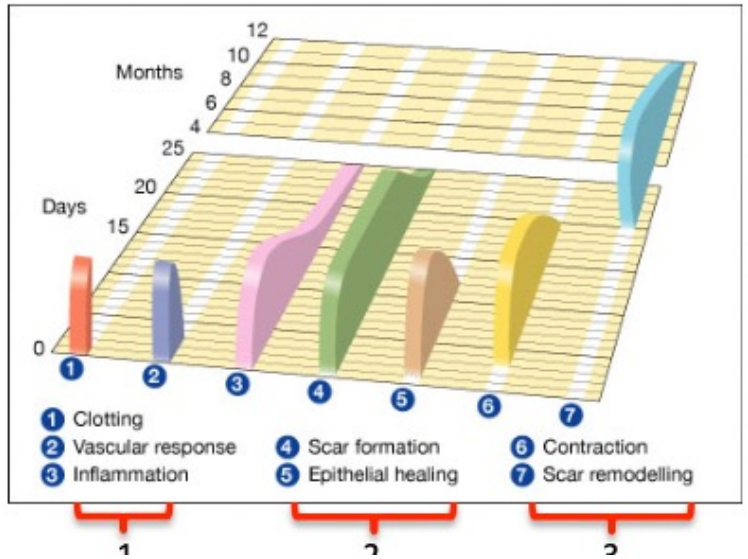
- **Phase I-II**: Granulation tissue forms (mixture of all required players: stem cells, immune cells, other cells, fibronectin, smaller collagens and proteoglycans)
- Phase I-II are the early repair phases, where tissue modelling starts. Here, critical gaps in the tissue are filled with **granulation tissue**. The sealing provides emergency tissue function – helps avoid apoptosis but is not perfect.
- The key steps here are: **angiogenesis** (via endothelial cells) and **matrix deposition** (via fibroblasts).
- Key cellular players are cells that form the components of the ECM (usually fibronectin and then later collagens) that give tissue strength and structure. Myofibroblasts generate much matrix and are highly contractive. They can migrate inward as mature cells form surrounding tissues, or differentiate from a progenitor cell.



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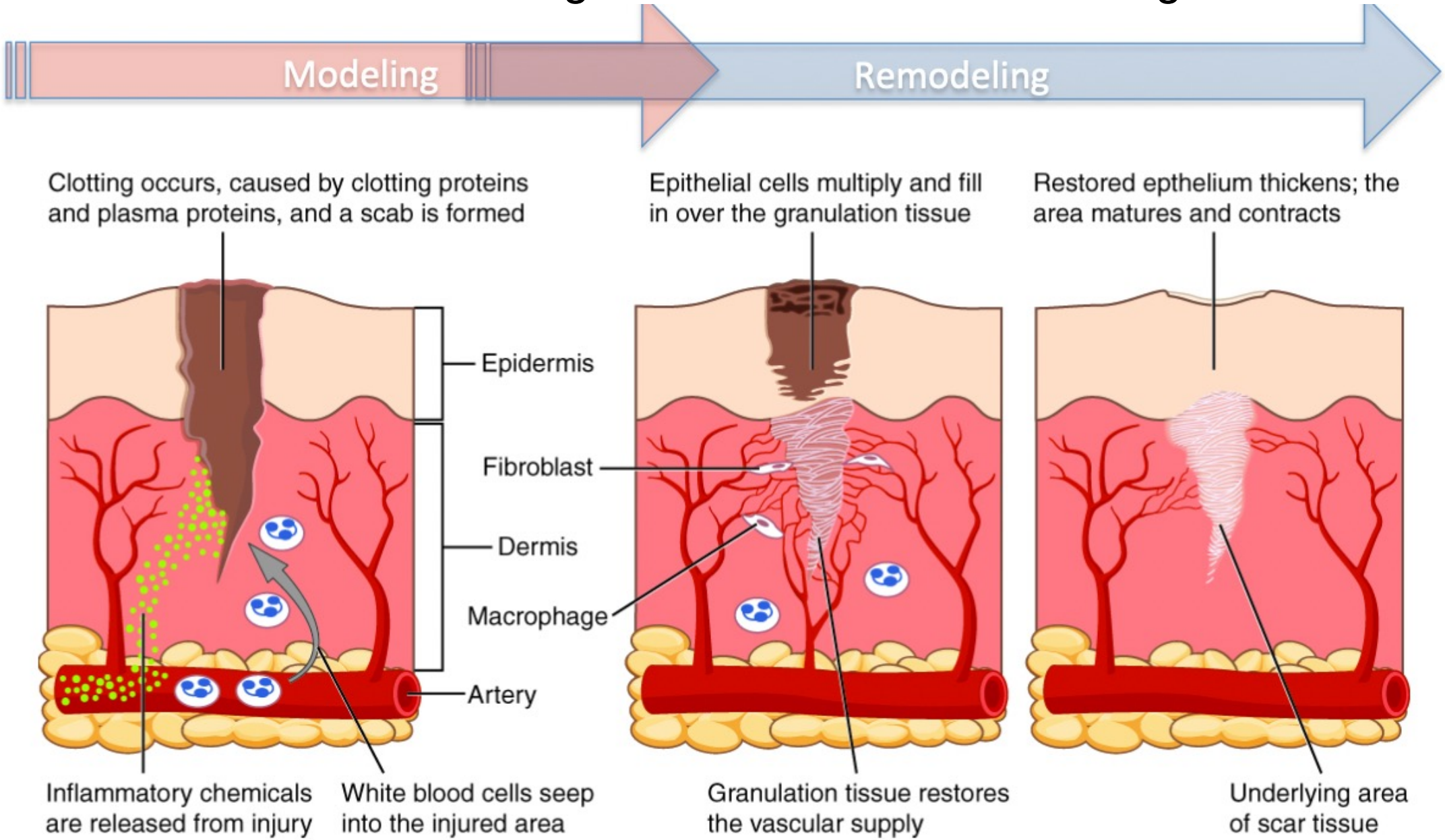
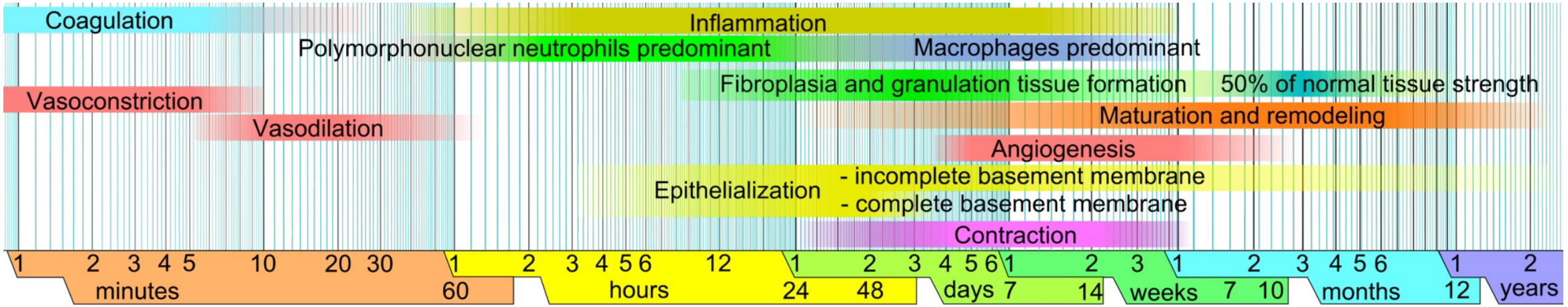


Introduction to Wound Healing - Overview

- **Phase I**: Haemostasis and inflammation - stop the bleeding and lay ground work for repair
- **Phase II**: Cell proliferation and tissue remodelling - return organism to function ASAP
- **Phase III**: Tissue remodelling - optimise tissue toward pre-injury status



Introduction to Wound Healing – Schematic representation of different stages of wound repair

A. **12 - 24 hours** after the injury a blood clot has formed. **Neutrophils** are the **first immune cells** to **enter** the **blood clot**.

B. **3 - 7 days** after injury most **neutrophils have undergone apoptosis**. But now many **macrophages are present**. Endothelial precursor cells migrate into the blood clot, proliferate and **form new blood vessels**.
   - **FIBROBLASTS** or their precursors **migrate** into the **sore tissue** where they **proliferate**, differentiate and **deposit extracellular matrix**. **Granulation tissue** is generated.
   - **KERATINOCYTES** (**skin cells**) **proliferate** and migrate along the injured dermis and over this provisional dressing of cells and matrix.

C. **1 - 2 weeks** after the injury, the **wound is completely filled** with **granulation tissue**. **Fibroblasts** have transformed into **myofibroblasts** (highly contractile cells), resulting in **wound contraction** and deposition of collagen. The **wound** is now **completely covered with a neo-epidermis** (new skin surface).